FATAL REACTION TO ACETAZOLAMIDE*†

BY

A. KRISTINSSON

Central Middlesex Hospital, London

ACETAZOLAMIDE is known to produce many minor side-effects when given for any length of time. Becker and Middleton (1955) have described the following in seventy patients receiving long-term acetazolamide for glaucoma: paresthesiae 61 per cent., gastrointestinal disturbances 49 per cent., excessive fatigue 16 per cent., urinary disturbances 4 per cent., hearing loss 3 per cent., leucopenia 3 per cent. The experience of Leopold, Eisenberg, and Yasuna (1955) was similar. Renal colic, stones, and crystallized acetazolamide in the renal tubules have been reported in 44 cases (Glushien and Fisher, 1956; Persky, Chambers, and Potts, 1956; Abeshouse and Applefeld, 1956; Gordon and Sheps, 1957; Barraquer and Escribano, 1957; Yates-Bell, 1958; Davies, 1959; Mackenzie, 1960). Skin rash (Spring, 1956) and serum sickness-like hypersensitivity (Moseley and Baroody, 1955) were found in three cases.

More serious reactions include agranulocytosis (Pearson, Binder, and Neber, 1955), fatal bone-marrow depression (Underwood, 1956), and two cases (one fatal) of thrombocytopenia (Reisner and Morgan, 1956; Bertino, Rodman, and Myerson, 1957).

This paper describes a third patient with a fatal reaction attributable to acetazolamide.

Case Report

The patient was a 54-year-old man of previous good health and temperate habits. He attended an Eye Hospital 26 days earlier with failing vision. Glaucoma was diagnosed and acetazolamide 500 mg. daily was prescribed. Thereafter he felt progressively weak and unwell with loss of appetite, and developed a rash. For 4 days before admission he had abdominal pain, nausea, vomiting and diarrhoea, and finally became delirious.

Examination.—He was confused and very ill; he was dehydrated and had peripheral circulatory failure. There was an erythematous rash all over the body. He was markedly jaundiced with hepatic foetor, flapping tremor, hiccough, and extreme tenderness in the right hypochondrium.

Investigations.—Hb 18 g./100 ml.; packed cell volume 55 per cent.; mean corpuscular haemoglobin concentration 33 per cent.; white blood cells 8,000/cu. mm.; erythrocyte sedimentation rate 49 mm./1 hr; sodium 141 mEq./l., potassium 4.9 mEq./l., chloride 106 mEq./l., bicarbonate 7 mEq./l.; blood-urea 242 mg./100 ml.; blood glucose 192 mg./100 ml.

Urine: no excess urobilinogen; increased red blood cells in the deposit.

Bilirubin 10.9 g./100 ml.; total protein 5.2 g./100 ml., gamma globulin 1 Kunkel unit; thymol turbidity 4 Kunkel units; alkaline phosphatase 44 King Armstrong units; serum alanine aminotransferase 180 Frankel units.

Leptospiral agglutination titre negative.

Electrocardiogram and chest x ray normal.

* Received for publication January 4, 1966.

† Address for reprints: Department of Medicine, Hammersmith Hospital, Ducane Rd., London, W.12.

Termination.—He did not respond to supportive treatment, remained anuric, and died 24 hours after admission.

Post-mortem Examination (Coroner's Pathologist: Dr. D. Teare) revealed an enlarged (2,400 g.) firm, tawny-coloured liver. A 6×3 cm. growth was found in the anterior mediastinum. The lungs showed gross terminal congestion. The kidneys, heart, and brain were macroscopically normal.

Microscopy showed intracellular and canalicular cholestasis of the liver with widespread patchy fatty infiltration. These changes were considered to be compatible with a diagnosis of drug intoxication. In the kidneys mild tubular degeneration was found with bile pigment and granular casts in the lumen. The anterior mediastinal tumour proved to be a localized focus of Hodgkin's disease.

Discussion

This patient died of cholestatic jaundice. There is no history of contact with jaundiced patients or of injections or transfusions. The only drug he had received was 13 g. acetazolamide in 26 days. The rash and the histology favour the diagnosis of drug-induced hypersensitivity and hepatitis. It seems almost certain that this drug was acetazolamide. There is no previous record of jaundice caused by acetazolamide, but it has been produced by sulphonamides (Sherlock, 1965) which are chemically closely related. It is important that this possibility be recognized, for acetazolamide is still freely used in the treatment of glaucoma.

Summary

A man, who died from hepatic coma and anuria, had taken 13 g. of acetazolamide for glaucoma in 26 days. A causal relationship is postulated.

I am indebted to Dr. M. W. McNicol, Central Middlesex Hospital, under whose care the patient was, to Dr. D. Teare, St. George's Hospital Medical School, who carried out the autopsy, and to Dr. R. Drury Central Middlesex Hospital, for his help in interpreting the histological findings.

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